The effect of esmolol on corrected-QT interval, corrected-QT interval dispersion changes seen during anesthesia induction in hypertensive patients taking an angiotensin-converting enzyme inhibitor

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Abstract

Background and objectives: The importance of minimizing the exaggerated sympathoadrenergic responses and QT interval and QT interval dispersion changes that may develop due to laryngoscopy and tracheal intubation during anesthesia induction in the hypertensive patients is clear. Esmolol decreases the hemodynamic response to laryngoscopy and intubation. However, the effect of esmolol in decreasing the prolonged QT interval and QT interval dispersion as induced by laryngoscopy and intubation is controversial. We investigated the effect of esmolol on the hemodynamic, and corrected-QT interval and corrected-QT interval dispersion changes seen during anesthesia induction in hypertensive patients using angiotensin converting enzyme inhibitors.

Methods: 60 ASA I–II patients, with essential hypertension using angiotensin converting enzyme inhibitors were included in the study. The esmolol group received esmolol at a bolus dose of 500 mcg/kg followed by a 100 mcg/kg/min infusion which continued until the 4th min after intubation. The control group received 0.9% saline similar to the esmolol group. The mean blood pressure, heart rate values and the electrocardiogram records were obtained as baseline values before the anesthesia, 5 min after esmolol and saline administration, 3 min after the induction and 30 s, 2 min and 4 min after intubation.

Results: The corrected-QT interval was shorter in the esmolol group \((p = 0.012)\), the corrected-QT interval dispersion interval was longer in the control group \((p = 0.034)\) and the mean heart rate was higher in the control group \((p = 0.022)\) 30 s after intubation. The risk of arrhythmia frequency was higher in the control group in the 4-min period following intubation \((p = 0.038)\).

Conclusion: Endotracheal intubation was found to prolong corrected-QT interval and corrected-QT interval dispersion, and increase the heart rate during anesthesia induction with propofol.
in hypertensive patients using angiotensin converting enzyme inhibitors. These effects were prevented with esmolol (500 mcg/kg bolus, followed by 100 mcg/kg/min infusion). During induction, the blood pressure tends to decrease with esmolol where care is needed.

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Efeito de esmolol sobre o intervalo QT corrigido e alterações da dispersão do intervalo QT corrigido observadas durante a indução da anestesia em pacientes hipertensos que receberam um inibidor da enzima conversora de angiotensina (IECA)

Resumo

Justificativa e objetivo: É óbvio a importância de minimizar as respostas simpatoadrenérgicas exageradas e o intervalo QT e a dispersão do intervalo QT que podem ocorrer por causa de laringoscopia e intubação traqueal durante a indução da anestesia em pacientes hipertensos. Esmolol diminui a resposta hemodinâmica à laringoscopia e à intubação. Porém, o efeito de esmolol sobre a redução do intervalo QT prolongado e a dispersão do intervalo QT induzida pela laringoscopia e intubação é controverso. Pesquisamos o efeito de esmolol sobre a hemodinâmica e o intervalo QT corrigido e as alterações da dispersão do intervalo QT observadas durante a indução da anestesia em pacientes hipertensos que receberam inibidores da enzima conversora de angiotensina (IECA).

Métodos: Foram incluídos no estudo 60 pacientes, estado físico ASA I-II, com hipertensão arterial essencial e que receberam IECA. O grupo esmolol recebeu uma dose em bolus de 500 mcg kg⁻¹, seguida por infusão contínua de 100 mcg kg⁻¹ min⁻¹ até o quarto minuto após a intubação. O grupo controle recebeu solução salina a 0,9%, semelhantemente ao grupo esmolol. Os valores da pressão arterial média e da frequência cardíaca e os registros do eletrocardiograma foram obtidos durante a fase inicial pré-anestesia, cinco minutos após a administração de esmolol e solução salina, três minutos após a indução e 30 segundos, dois minutos e quatro minutos após a intubação.

Resultados: O intervalo QT corrigido foi menor no grupo esmolol ($p = 0,012$), o intervalo de dispersão do intervalo QT corrigido foi maior no grupo controle ($p = 0,034$) e a frequência cardíaca média foi maior no grupo controle ($p = 0,022$) 30 segundos após a indução. O risco da frequência de arritmia foi maior no grupo controle no quarto minuto após a intubação ($p = 0,038$).

Conclusão: Descobrimos que a intubação traqueal prolonga o intervalo e a dispersão do intervalo QT corrigido e aumenta a frequência cardíaca durante a indução da anestesia com propofol em pacientes hipertensos que receberam IECA. Esses efeitos foram prevenidos com esmolol (bolus de 500 mcg kg⁻¹, seguido de 100 mcg kg⁻¹ min⁻¹ de infusão). Durante a indução, a pressão tende a diminuir com esmolol. Portanto, cuidados são necessários.

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Introduction

A prolonged QT interval and corrected-QT interval (QTC) combined with QT interval dispersion (QTD) and corrected-QTD (QTCd) are known to increase the incidence of fatal arrhythmias such as polymorphic ventricular arrhythmia or ventricular fibrillation and cause sudden deaths by causing cardiac irritability. An increase in sympathetic activity and plasma catecholamine concentrations is known to cause prolongation of the QT interval and QT dispersion. Laryngoscopy and tracheal intubation have been shown to cause hyperdynamic responses such as hypertension, tachycardia, arrhythmia and prolongation of the QT interval. Although the observed hemodynamic responses are temporary, they may cause serious complications such as cerebral hemorrhage, arrhythmia, myocardial ischemia or even infarction in the presence of accompanying cerebrovascular disease, coronary artery disease or hypertension.

Essential hypertension is the most common accompanying disorder in patients admitted for surgery. The disturbed cardiovascular homeostasis in hypertensive patients has been shown to cause a sympatho-vagal imbalance characterized by decreased vagal modulation and increased sympathetic activity. The response to laryngoscopy is significantly different in hypertensive patients compared to normotensive patients. The blood pressure changes that develop immediately following anesthesia induction are much larger in hypertensive patients. These patients have marked hypotension with induction and marked hypertension with laryngoscopy and intubation. A blood
pressure fluctuation of more than 20% in hypertensive patients has been shown to be associated with perioperative complications. The most common cause of sudden cardiac death in hypertensive cases unaccompanied by coronary artery disease has been reported to be ventricular arrhythmias\textsuperscript{10} and QT prolongation in hypertensive patients has been found to be associated with sudden death.\textsuperscript{11} The importance of minimizing the exaggerated sympatho-adrenergic response and QT interval and QT changes during anesthesia induction in the hypertensive patient group is therefore clear. To prevent such detrimental events different classes of drugs have been used. Esmolol is a cardioselective beta-adrenergic blocking agent with a rapid onset of action and quite short elimination half-time. It is known to decrease the hemodynamic response to laryngoscopy and intubation.\textsuperscript{12,13} However, the results of the limited number of studies where the effect of esmolol in decreasing the prolonged QT interval and QT as induced by laryngoscopy and intubation are controversial.

There is a consensus on continuing antihypertensive medication until the morning of the day of surgery at present. However, the use of angiotensin converting enzyme inhibitors (ACEIs) is debated due to the potential of developing hypotension resistant to vasopressors. Some authors report the need to continue,\textsuperscript{4} while others believe they should be discontinued.\textsuperscript{15} We did not find any studies on the effect of esmolol on the hemodynamic and QT interval and QT changes seen during anesthesia induction in hypertensive patients taking a ACEIs.

The aim of this study was to investigate the effect of esmolol on the hemodynamic, QTc and QTcD changes during anesthesia induction seen in hypertensive patients taking a ACEIs.

**Methods**

A total of 60 patients aged 20–65 years and taking a ACEIs with regulated essential hypertension, who were about to undergo elective surgery were included in this prospective, randomized, double-blind study after obtaining ethic committee approval and written patient consent. Patients with unstable angina, severe conduction disorder or arrhythmia, chronic obstructive pulmonary disease, cardiac failure and cardiac valve disease, those using drugs known to prolong the QT interval (such as tricyclic antidepressants, quinidine, disopyramide, sotolol, Ca channel blockers), patients with electrolyte disorders or abnormal blood coagulation profiles, patients known to be hypersensitive to the medication to be used and pregnant women were excluded from the study. Patients to whom the intubation could be difficult and those who were intubated after several attempts were not included in the study. Information was provided on the method to be used and verbal and written consent were obtained from the patients on the preoperative visit the day before surgery. Antihypertensive treatment was continued until the morning of surgery but no premedication was administered.

Following vascular access with a 20G intracath in the operating room, the patients were monitored for pulse oximetry (Draeger infinity delta monitor, USA), non-invasive blood pressure (Draeger infinity delta monitor, USA) and a 12-lead electrocardiogram (ECG) device (Trismed, Cardipia 400). The initial heart rate (HR), mean blood pressure (MBP) values and 12-lead ECG were recorded. The patients were prospectively randomized by computer to one of the esmolol and control groups. Esmolol (Breviblock, Eczacıbaşı-Baxter Co) was administered as a 100 mcg/kg/min infusion following a 500 mcg/kg bolus dose (in 5 mL of volume, within 30 s) in the esmolol group. The esmolol infusion was continued up to 4 min after the intubation. A bolus and infusion administration similar to the esmolol group was performed with 0.9% saline in the control group. Anesthesia was induced with 2 mg/kg propofol and 1 mcg/kg fentanyl 5 min after esmolol or saline induction in both groups. Patients were intubated within 3 min of vecuronium (1 mg/kg) administration by an experienced anesthetist and the procedure lasted 20 s on average. Patients whose MBP decreased to below 55 mmHg and the HR to below 50/min were administered 5 mg ephedrine and 0.5 mg atropine. The esmolol infusion was discontinued if there was no response to medication. The MBP, HRS and ECG (at a sweep rate of 50 mm/s) of the patients were recorded as a baseline value before the anesthesia (T0), 5 min after esmolol or saline administration (T1), 3 min after induction medication (T2), 30 s after the intubation (T3), 2 min after the intubation (T4), and 4 min after the intubation (T5) for a total of 6 times.

The study drugs were prepared by an anesthetist who was not included in the study and did not know the patient groups. The records were kept by another anesthetist who again did not know the patient groups. ECG records were evaluated by a cardiologist who did not know the patient groups. The distance from the start of the QRS complex to the end of the T wave was accepted as the QT interval. When the T wave was bi-notched, the end of the T wave was accepted as the point where the first wave’s extension reached the isoelectric line when the second notch was smaller than 50% of the first notch and as the point where the second wave reached the isoelectric line if it was larger than 50% of the first notch. Three QT distances were measured for each derivation and averaged. QT intervals corrected for HR (QTc) were calculated for all derivations using Bazett’s formula \((QTc = QT_{ms}/\sqrt{RR_{ms}})^{1/2}\). The average of the QTc values of three consecutive heartbeats at each derivation was accepted as the QTc interval of that derivation. QTcD was calculated as the difference between the longest QT distance and the shortest QT distance at each interval while QTcD was calculated as the difference between the longest and shortest QTc values.

Statistical analysis was performed with the "SPSS 16.0 for Windows software" (SPSS, Inc., Chicago, IL, USA). Assuming an alpha level of 0.05 and a power of 0.80, a minimum of 21 patient in each group were required to detect a mean difference of 20 ms and 22 ms of standard deviation for the QTc interval between the two groups. The differences between the groups were evaluated with the "independent samples t-test" or "chi-square" tests. The MBP, HR, QTc interval and QTcD changes in each group were evaluated with the analysis of variance test (with the Bonferroni correction). A \(p\) value less than 0.05 was accepted as statistically significant.
## Results

There was no difference between the groups regarding demographic data (Table 1). The mean basal blood pressure, HR, QTc interval and QTcD values were similar in the two groups.

The MBP was lower in the esmolol group than the control group at the T1 (84.1 ± 17.4 vs. 98.2 ± 14.7), T2 (62.8 ± 8.5 vs. 87.7 ± 11.5) and T3 (75.4 ± 6.8 vs. 91.3 ± 21.2) measurement times (Fig. 1). There was a marked decrease in MBP levels compared to baseline at all measurement times after the induction drugs were administered (T2) in the control group (T2: *p* = 0.001; T3: *p* = 0.020; T4: *p* = 0.025; T5: *p* = 0.001) and at all measurement times after esmolol was administered (T1) in the esmolol group (T1: *p* = 0.001; T2: *p* = 0.001; T3: *p* = 0.001; T4: *p* = 0.002; T5: *p* = 0.001). The esmolol group, in contrast to the control group, showed a markedly larger decrease in MBP following propofol induction (T2) (Fig. 1) (*p* = 0.001).

Comparison of mean HR values showed a significant difference between the groups in the measured values 30 s after intubation (T3). The mean HR was markedly higher 30 s after intubation (T3) in the control group (84.2 ± 15.6 vs. 93.2 ± 13.9, *p* = 0.022). The HR in the esmolol group was lower than the baseline value at all measurement times except T3 (T1: *p* = 0.007; T2: *p* = 0.001; T4: *p* = 0.015; T5: *p* = 0.001) while it was similar to the baseline value 30 s after intubation. The HR values in the control group were lower than baseline at the T2 measurement time (*p* = 0.003) and higher than the baseline at T3 (Fig. 2) (*p* = 0.001).

The mean basal QTc values of the patients were similar in the 2 groups. The baseline QTc values were higher than 440 ms in 12 (40%) patients from the esmolol group and 10 (33%) patients from the control group with no difference between the groups (*p* > 0.05). The QTc interval was markedly shorter in the esmolol group than the control group 30 s after intubation (T3) (439.7 ± 27.8 vs. 458.7 ± 29.3 *p* = 0.012). The QTc interval duration shortened slightly after esmolol administration but this was not statistically significant. The QTc interval was similar to the baseline at all measurement times (*p* = 0.618). The QTc interval values 30 s (T3) and 2 min (T4) after intubation in the control group were longer than both baseline values (*p* = 0.001, *p* = 0.001) and the time at T1 (*p* = 0.001, *p* = 0.003) (Fig. 3).

The mean baseline QTcD values of the patients were similar in the two groups. The QTcD interval was markedly longer in the control group than the esmolol group 30 s after intubation (T3) (*p* = 0.034). The QTcD interval values in the esmolol group did not show a statistically significant change at any measurement time (*p* = 0.061). The QTcD values in the control group were longer than the baseline after the induction drugs (T2) and 2 min after intubation (T3) and longer than

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**Table 1** Demographic and clinical data (mean ± SD).

<table>
<thead>
<tr>
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<th>Esmolol (n = 30)</th>
<th>Control (n = 30)</th>
<th>p-value</th>
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<tr>
<td>Age (years)</td>
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<td>57.9 ± 6.8</td>
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<tr>
<td>Gender (female/male)</td>
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<td>9/21</td>
<td>0.559</td>
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<tr>
<td>ASA (I/II)</td>
<td>16/14</td>
<td>21/9</td>
<td>0.184</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>159.8 ± 7.6</td>
<td>162.2 ± 7.7</td>
<td>0.120</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73.1 ± 14.4</td>
<td>78.2 ± 13.2</td>
<td>0.184</td>
</tr>
</tbody>
</table>

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**Figure 1** Mean **“blood pressure”** values in the esmolol and control groups. T0, basal value; T1, 5 min post-esmolol administration; T2, 2 min post-induction drugs administration; T3, 30 s post-intubation; T4, 2 min post-intubation; T5, 4 min post-intubation. *p* = 0.001, when the two groups are compared; "p" = 0.001, when compared with the baseline; "p" = 0.002, when compared with the baseline; "p" = 0.001, when compared with the baseline; "p" = 0.020, when compared with the baseline; ""p" = 0.025, when compared with the baseline.

**Figure 2** Mean **“heart rate”** values in the esmolol and control groups. T0, basal value; T1, 5 min post-esmolol administration; T2, 2 min post-induction drugs administration; T3, 30 s post-intubation; T4, 2 min post-intubation; T5, 4 min post-intubation. *p* = 0.022, when the two groups are compared; "p" < 0.005, when compared with the baseline.
changes in a hypertensive patient group taking ACEIs. The QTc and QTcD prolongation following intubation was kept under control with 500 mcg/kg bolus esmolol followed by a 100 mcg/kg/min infusion. Esmolol also stopped the increased HR following intubation. However, esmolol led to a marked decrease in blood pressure during induction.

As far as we know, our study is the first to investigate the effect of esmolol on hemodynamic responses induced by laryngoscopy and tracheal intubation and also on the QT interval and QTcD in a hypertensive patient group taking ACEIs. Although there have been many studies on the suppression of the intubation-related hemodynamic responses with esmolol, there is no consensus on the optimum time and route of administration. A large meta-analysis by Figueredo and Garcia-Fuentes\textsuperscript{15} on the effectiveness of esmolol for the suppression of intubation-related hemodynamic responses in 2900 patients evaluated 11 different regimes and doses of esmolol in a systematic manner. The result was that esmolol was effective in suppressing intubation-related hemodynamic responses but it carried a dose-dependent risk of hypotension during anesthesia induction. The most effective dose with a lower incidence and severity of side effects was a 500 mcg/kg bolus dose followed by a continuous infusion of 200 or 300 mcg/kg/min. We used a 500 mcg/kg bolus dose of esmolol followed by a 100 mcg/kg/min continuous infusion. The infusion dose was halved for two reasons. The first was the high rate of hypotension in our pilot study with infusion doses of 200 mcg/kg/min. The second reason was the use of propofol as the induction agent. Although there are studies showing that propofol prolongs the QT interval,\textsuperscript{16,17} it is generally accepted that propofol has no or a little effect on the QT interval.\textsuperscript{18,19} We therefore preferred the use of propofol for induction instead of volatile agents or thiopental that are known to prolong the QT interval. However, propofol is also known to be able to decrease blood pressure\textsuperscript{20,21} and cause bradycardia\textsuperscript{22} by decreasing systemic vascular resistance. Korpinen et al.\textsuperscript{23} have reported that a propofol--esmolol combination causes hemodynamic depression in their study where they investigated the electrocardiographic and hemodynamic effects of esmolol combined with methohexital and propofol during anesthesia induction. Taking into account that our study would be performed on the hypertensive patient group where hemodynamic fluctuations are more prominent, we decreased the infusion dose so as not to cause more cardiovascular depression during esmolol usage. The esmolol doses we used prevented the increase in HR following intubation but preserved the beginning HR values in the control group. However, the decrease observed in MBP during induction is much higher than the decrease in the control group and noteworthy. We believe that the vasodilation-causing effect of both propofol and the ACE inhibitor in the hypertensive patient group becomes potentiated with esmolol in the hypertensive patient group. However, controlled studies are needed to verify this opinion. It may be useful to decrease propofol dose to avoid deep hypotension during induction in hypertensive patients taking ACEIs. Weisenberg et al.\textsuperscript{24} have recently published an article where they investigated the hemodynamic changes caused by anesthesia induction with propofol at 4 different doses in patients using a ACEIs. They decided that a dose of 1.3 mg/kg decreased

Discussion

In this study we investigated the effect of esmolol on the induction hemodynamics, and QTc interval and QTcD

Figure 3 Mean “QTc” values in the esmolol and control groups. T0, basal value; T1, 5 min post-esmolol administration; T2, 2 min post-induction drugs administration; T3, 30 s post-intubation; T4, 2 min post-intubation; T5, 4 min post-intubation. $^p$ = 0.012, when the two groups are compared; $^p$ = 0.001, when compared with the baseline; $^p$ = 0.001, when compared with the T1; $^p$ = 0.003, when compared with the baseline.

Figure 4 Mean “QTD” values in the esmolol and control groups. T0, basal value; T1, 5 min post-esmolol administration; T2, 2 min post-induction drugs administration; T3, 30 s post-intubation; T4, 2 min post-intubation; T5, 4 min post-intubation. $^p$ = 0.034, when the two groups are compared; $^p$ = 0.003, when compared with the baseline; $^p$ = 0.001, when compared with the baseline; $^p$ = 0.006, when compared with the baseline; $^p$ = 0.036, when compared with the baseline.

both the baseline and T1 (post-esmolol) levels 30 s after intubation (T3) (Fig. 4).

There was no need to use atropine in the patients while ephedrine was required in 3 patients in the esmolol group. The esmolol infusion did not need to be discontinued in any patient. The incidence of arrhythmia development was higher in the 4 min after intubation in the control group ($p = 0.038$). Unifocal ventricular extrasystoles developed in 2 patients from the esmolol group while multifocal ventricular extrasystoles developed in 4 patients, ventricular bigeminy in 1 patient, and unifocal ventricular extrasystoles in 3 patients from the control group.
hemodynamic instability. However in this study bispectral index monitoring was not used and optimal hemodynamic control was assumed synonymous with optimal anesthesia includes analgesia and amnesia. More studies are needed to determine the optimum dose during the use of esmolol with propofol induction in hypertensive patients taking ACEIs.

It is known that there is a close relationship between essential hypertension and the autonomous nervous system and that the frequency of cardiac arrhythmias increases in patients with disturbed QT dynamics.

Increased QTd in hypertensive patients has been found to be associated with sudden death and various anti hypertensive drugs have been shown to decrease the incidence of QTd and arrhythmia. Taking into account that laryngoscopy and sympathetic activation also prolong the QT interval and QTd, it may be clinically significant to use methods that decrease the QTd in hypertensive patients to prevent the sympatho-adrenergic responses induced by laryngoscopy and tracheal intubation. Beta-blockers known to decrease the cardiovascular responses to sympathetic stimuli may decrease the development of arrhythmia in this aspect. Various results have been reported regarding the effect of esmolol on the QT interval induced by laryngoscopy and intubation.

Korpinnen et al.

have reported that esmolol combined with propofol and alfentanil induction in otolaryngology surgery shortens the QTc interval. The same investigator also reported in two separate studies that esmolol shortens the QTc interval prolongation seen following intravenous anesthetic usage but does not shorten the prolongation seen following intubation.

Another study by the same investigator combining esmolol with metohexitol or propofol induction has reported results similar to these two studies. However, it is noteworthy that some of these studies used succinyl choline, while some used thiopental, and some anticholinergic premedication. These agents are known to prolong the QT interval. Erdil et al.

have published a study where they investigated the effect of esmolol on the QTc interval changes seen during anesthesia induction in coronary artery disease patients. This study combined etomidate, fentanyl and vecuronium induction with esmolol and reported that esmolol kept the hemodynamic responses to intubation and the QTc interval prolongation following intubation under control. Esmolol was used at a bolus dose of 1000 mcg/kg followed by an infusion of 250 mcg/kg/min and no cardiovascular depression developed in the patients despite this relatively high dose. The investigators felt this was due to the use of agents with minimal cardiovascular effects during induction. In our study we found that the prolonged QTc and QTcD values that started with anesthesia induction and peaked with intubation in the control group were prevented with esmolol. Besides, arrhythmia occurrence frequency after entubation was also decreased with esmolol. Recently, Kaneko et al.

investigated the effect of landiolol, an ultra-short acting β1 adrenoceptor antagonist, on QT interval and QR dispersion. Similar to our results, they found that landiolol prevents increase in QT, QTc, QTD, and QTcD during and after tracheal intubation.

We observed that the basal QTc values of our patients were relatively high (439.4 ± 29.2 and 428.1 ± 25.4). These high values may be due to our patients being hypertensive with high sympatho-adrenal tonus. In addition, the lack of premedication may also have contributed to the sympatho-adrenal tonus increase by causing anxiety.

A limitation of our study is that we did not compare patients who continued taking ACEIs with those who discontinued. As we remarked before, there is no consensus on whether ACEIs should be continued until the morning of surgery due to the potential for the development of hypotension resistant to vasopressors. Therefore we cannot definitively recommend whether ACEIs should be continued or discontinued especially if esmolol infusion is used during anesthesia induction. However our results suggest that ACEIs should be continued.

In conclusion, endotracheal intubation during anesthesia induction with propofol was found to prolong QTc and QTcD and increase the HR in hypertensive patients using ACEIs while esmolol infusion at a bolus of 500 mcg/kg followed by 100 mcg/kg/min infusion prevented these responses. Furthermore it was also found that the blood pressure tends to decrease with esmolol during induction and care is needed.

Conflicts of interest

The authors declare no conflicts of interest.

References